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Katharina Feil, Jens Claaßen, Stanislavs Bardins, et al.

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Effect of chlorzoxazone in patients with downbeat nystagmus

A pilot trial



Katharina Feil, MD*
Jens Claaßen, MD*
Stanislavs Bardins
Julian Teufel, MD
Siegbert Krafczyk
Erich Schneider, PhD
Roman Schniepp, MD,
MD
Klaus Jahn, MD
Roger Kalla, MD
Michael Strupp, MD

Correspondence to
Dr. Feil:
katharina.feil@med.uni-
muenchen.de

ABSTRACT

Objective: Downbeat nystagmus (DBN) is the most frequent form of acquired persisting fixation nystagmus with different symptoms such as unsteadiness of gait, postural instability, and blurred vision with reduced visual acuity (VA) and oscillopsia. However, different symptomatic therapeutic principles are required, such as 3,4-diaminopyridine and 4-aminopyridine, that effectively suppress DBN. Chlorzoxazone (CHZ) is a nonselective activator of small conductance calcium-activated potassium (SK) channels that modifies the activity of cerebellar Purkinje cells. We evaluated the effects of this agent on DBN in an observational proof-of-concept pilot study.

Methods: Ten patients received CHZ 500 mg 3 times a day for 1 or 2 weeks. Slow-phase velocity of DBN, VA, postural sway, and the drug's side effects were evaluated. Recordings were conducted at baseline, 90 minutes after first administration, and after 1 or 2 weeks.

Results: Mean slow-phase velocity significantly decreased from a baseline of $2.74^\circ/\text{s} \pm 2.00$ to $2.29^\circ/\text{s} \pm 2.12$ (mean \pm SD) 90 minutes after first administration and to $2.04^\circ/\text{s} \pm 2.24$ ($p < 0.001$; post hoc both $p = 0.024$) after long-term treatment. VA significantly increased and postural sway in posturography showed a tendency to decrease on medication. Fifty percent of patients did not report any side effects. The most common reported side effect was abdominal discomfort and dizziness.

Conclusions: The treatment with the SK-channel activator CHZ is a potentially new therapeutic agent for the symptomatic treatment of DBN.

Classification of evidence: This study provides Class IV evidence that CHZ 500 mg 3 times a day may improve eye movements and visual fixation in patients with DBN. *Neurology*® 2013;81:1152-1158

GLOSSARY

4-AP = 4-aminopyridine; **CHZ** = chlorzoxazone; **3,4-DAP** = 3,4-diaminopyridine; **DBN** = downbeat nystagmus; **EA2** = episodic ataxia type 2; **PC** = Purkinje cell; **SK** = small conductance calcium-activated potassium; **SPV** = slow-phase velocity; **VA** = visual acuity.

Downbeat nystagmus (DBN) is the most frequent form of acquired persisting fixation nystagmus.¹⁻³ The most common symptoms are unsteadiness of gait, postural instability, blurred vision with reduced visual acuity (VA), and vertical oscillopsia.^{1,2} DBN is most often caused by impaired function of the cerebellar flocculus/paraflocculus.⁴ The etiology is diverse. In approximately 40% of patients, no underlying pathology can be found.³ Of the different medications that have been used to treat DBN,⁵ GABAergic, glutamatergic, and cholinergic drugs showed only moderate success.⁵ However, 3,4-diaminopyridine (3,4-DAP) and 4-aminopyridine (4-AP) effectively suppress DBN.⁵

The small conductance calcium-activated potassium (SK) channel activator chlorzoxazone (CHZ) reduced burst-like firing and thereby decreased irregular Purkinje cell (PC) firing in P/Q calcium-channel *CACNA1a*^{S218L} mutants.⁵⁻⁸ A mechanism similar to that of Kv1.5 potassium-channel blockers⁵⁻⁷ is assumed for the effects of aminopyridines in episodic ataxia type 2 (EA2). CHZ has already been used as a centrally acting agent for painful musculoskeletal conditions and muscle spasm,^{9,10} and is an over-the-counter drug approved by the US Food and Drug Administration¹⁰ (for reference, see <http://www.drugs.com/pro/chlorzoxazone.html>). Based on the

*These authors contributed equally to this work.

From the Department of Neurology and German Center for Vertigo and Balance Disorders, University Hospital Munich, Campus Grosshadern, Munich, Germany.

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Table 1 Clinical characteristics of patients with DBN

Patient	Sex	Age, y	Etiology	Age at onset of disease, y	Duration of disease, y	Brain MRI findings	Neuro-ophthalmologic findings (apart from DBN) ^a	Polyneuropathy (impaired ankle reflexes and/or paresthesia)	BVP	Romberg	Gait
1	Male	76	Idiopathic	62	14	Normal	1, 2, 3, 5 (Bilateral), 6, 7	No	No	Normal	Normal
2	Male	71	Idiopathic	63	8	Normal	1, 2, 3, 6, 7, Hypometric saccades downward	No	No	Pathologic	Ataxic
3	Female	51	Idiopathic	49	2	Microangiopathy	1, 2, 6, Hypermetric saccades, complete OTR	No	No	Normal	Normal
4	Male	56	Secondary (cerebellar degeneration)	48	8	Cerebellar atrophy	1, 2, 6, 7	No	No	Normal	Normal
5	Female	73	Idiopathic	67	6	Normal	1, 2, 6, 7	Yes	No	Pathologic	Ataxic
6	Male	79	Idiopathic	78	1	Normal	1, 2, 5 (Bilateral), 6, 7	No	Yes	Normal	Normal
7	Male	73	Secondary (cerebellar degeneration)	68	5	Atrophy of vermis	1, 2, 3, 5 (Bilateral), 6, 7	Yes	No	Pathologic	Ataxic
8	Female	78	Secondary (cerebellar degeneration)	72	6	Microangiopathy and cerebellar atrophy	1, 2, 4, 5 (Bilateral), 6, 7	Yes	No	Pathologic	Ataxic
9	Female	59	Idiopathic	54	5	Normal	1, 2, 6, 7, SVV deviation	No	No	Normal	Normal
10	Female	65	Idiopathic	63	2	Normal	1, 2, 3, 6, SVV deviation	Yes	No	Normal	Normal

Abbreviations: BVP = bilateral vestibulopathy; DBN = downbeat nystagmus; OTR = ocular tilt reaction; SVV = subjective visual vertical.

Shown are clinical characteristics of the patients with DBN, categorized by patient number, sex, age, neuro-ophthalmologic findings, other neurologic symptoms, MRI findings, etiology of DBN, and duration of disease (since the beginning of symptoms).

^a Findings: 1 = saccadic smooth pursuit; 2 = gaze-evoked nystagmus; 3 = head-shaking nystagmus; 4 = rebound nystagmus; 5 = pathologic head-thrust test (uni- or bilateral); 6 = impaired visual fixation suppression of the vestibulo-ocular reflex; 7 = pathologic optokinetic reflex.

above-mentioned theoretical and pharmacologic effect and in particular its action on PCs, the effectiveness in patients with DBN was tested.

METHODS Level of evidence. The aim of this Class IV evidence study was to evaluate the effect of CHZ 500 mg 3 times a day orally in terms of eye movements, postural sway, and visual fixation in patients with DBN.

Standard protocol approvals, registration, and patient consents. This pilot trial was only an observational study. All patients gave their informed consent for the compassionate use of CHZ.

Concept of the pilot trial. Ten patients (aged 48–78 years, 5 females; for further details, see table 1) received 500 mg of CHZ 3 times a day for 1 or 2 weeks. Measurements were conducted at baseline, after first drug administration, and after 1 to 2 weeks of treatment. Measurements were performed 90 minutes after first administration as peak levels of CHZ may be reached approximately 1 to 2 hours after oral administration.¹¹ After this first dose of the medication, the patients took another tablet in the evening; from day 2 of the observational period, the patients had the full dosage of CHZ 500 mg 3 times a day. Eye movements were recorded with 3-dimensional video-oculography (EyeSeeCam) (see reference 12). VA was measured using the Snellen chart positioned at a distance of 6 m and was specified as a decimal. Thus, optimal VA is 1.0. Posturographic measurements were conducted in the upright position with eyes open and head extended backward (30°). The 2 conditions included standing either on firm ground (condition 1) or on a slab of foam rubber (condition 2) (see reference 13). The body sway of 30 seconds of the posturographic measurement provided the sway path values (m/min). For safety reasons, blood testing of liver enzymes, sodium, potassium, creatinine, and urea was performed. The patients used the 28-item Vestibular Disorders Activities of Daily Living Scale¹⁴ to determine their functional burden of disease on a 10-point scale at baseline and during treatment.

Statistical analysis. Figures were designed using Prism version 5 (GraphPad Software, Inc., La Jolla, CA). Statistical analysis was done using SPSS version 20 (IBM Corp., Armonk, NY). Data were not normally distributed; hence, nonparametric statistical tests were performed. To look for differences between baseline and the 2 measurements under medication, the Friedman test with χ^2 test statistics was applied. For individual post hoc comparisons, the nonparametric Wilcoxon test statistics with Bonferroni correction were applied. In the eye-movement data, slow-phase velocity (SPV) of vertical eye movements was the dependent variable. DBN indicated by mean SPV (degrees/s) appears as a positive value, whereas the absence of DBN is a near zero value. For VA and postural sway, the same statistical analysis as in SPV was applied. The significance level was set to 5%. Patients who did not complete the long-term treatment were not included in the baseline data for the long-term treatment analysis.

RESULTS Effects of CHZ on SPV of DBN. Mean SPV decreased from baseline of $2.74^\circ/\text{s} \pm 2.00$ (mean \pm SD) to $2.29^\circ/\text{s} \pm 2.12$ after the first administration of CHZ 500 mg and from $3.09^\circ/\text{s} \pm 2.19$ to $2.04^\circ/\text{s} \pm 2.24$ after long-term treatment. There was a significant overall decrease (Friedman test with χ^2 statistics = 8.86, $p < 0.001$, $n = 7$) with a significant post hoc difference between baseline and 90 minutes after first administration ($p = 0.024$) as well as after long-term

treatment ($p < 0.001$). The patients showed a mean Δ SPV of 28% after first administration and 44% after long-term treatment. Mean SPV decreased by $\geq 40\%$ in 40% of patients after first administration and in 4 of 7 subjects after long-term treatment. The remainder of the patients showed a 10% to 30% decrease of mean SPV after long-term treatment (see figure 1 and figure 2, A and B). In total, 50% of patients had a decrease of mean SPV of $\geq 30\%$ and 30% of patients of $\geq 50\%$ after the first administration of CHZ.

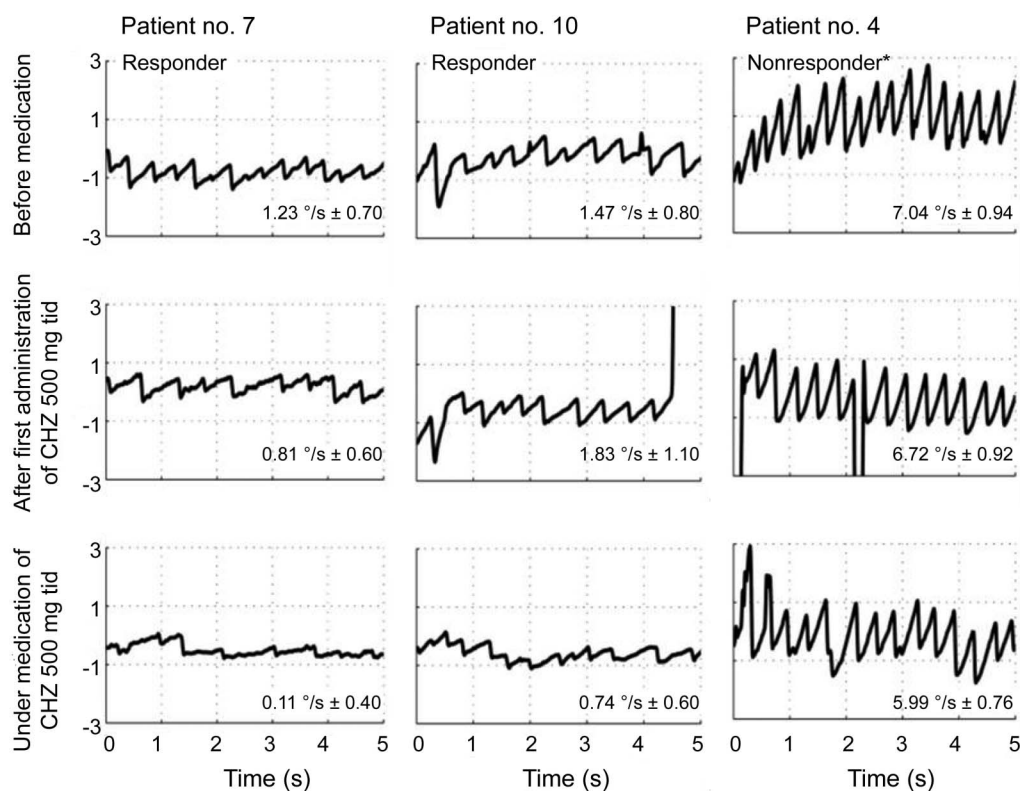
Effects of CHZ on VA. VA increased from 0.73 ± 0.24 at baseline to 0.84 ± 0.20 after first administration and from 0.72 ± 0.24 to 0.75 ± 0.25 after long-term treatment. There was a significant overall increase (Friedman test with χ^2 statistics = 7.00, $p = 0.047$, $n = 7$) with a significant post hoc difference between baseline and VA 90 minutes after administration of CHZ ($p = 0.01$) as well as between baseline and after long-term treatment ($p = 0.02$) (see figure 2C).

Effects of CHZ on postural sway. In condition 1, sway path decreased from 1.68 ± 0.95 m/min to 1.26 ± 0.65 m/min 90 minutes after first administration and from 1.36 ± 0.63 m/min to 1.00 ± 0.33 m/min after long-term treatment. There was a marginal

significant overall decrease (Friedman test with χ^2 statistics = 6.00, $p = 0.05$, $n = 4$) with a marginal significant post hoc difference between baseline and first administration ($p = 0.08$) but no significance between baseline and after long-term treatment ($p = 0.12$) (see figure 2D). In condition 2, sway path decreased from 3.80 ± 2.11 m/min to 3.17 ± 2.07 m/min and from 4.31 ± 2.29 m/min to 2.81 ± 1.31 m/min. There was a significant overall decrease (Friedman test with χ^2 statistics = 6.50, $p = 0.039$, $n = 4$) with a marginal significant post hoc difference of sway between baseline and first administration ($p = 0.08$) but no significance between baseline and long-term treatment ($p = 0.435$).

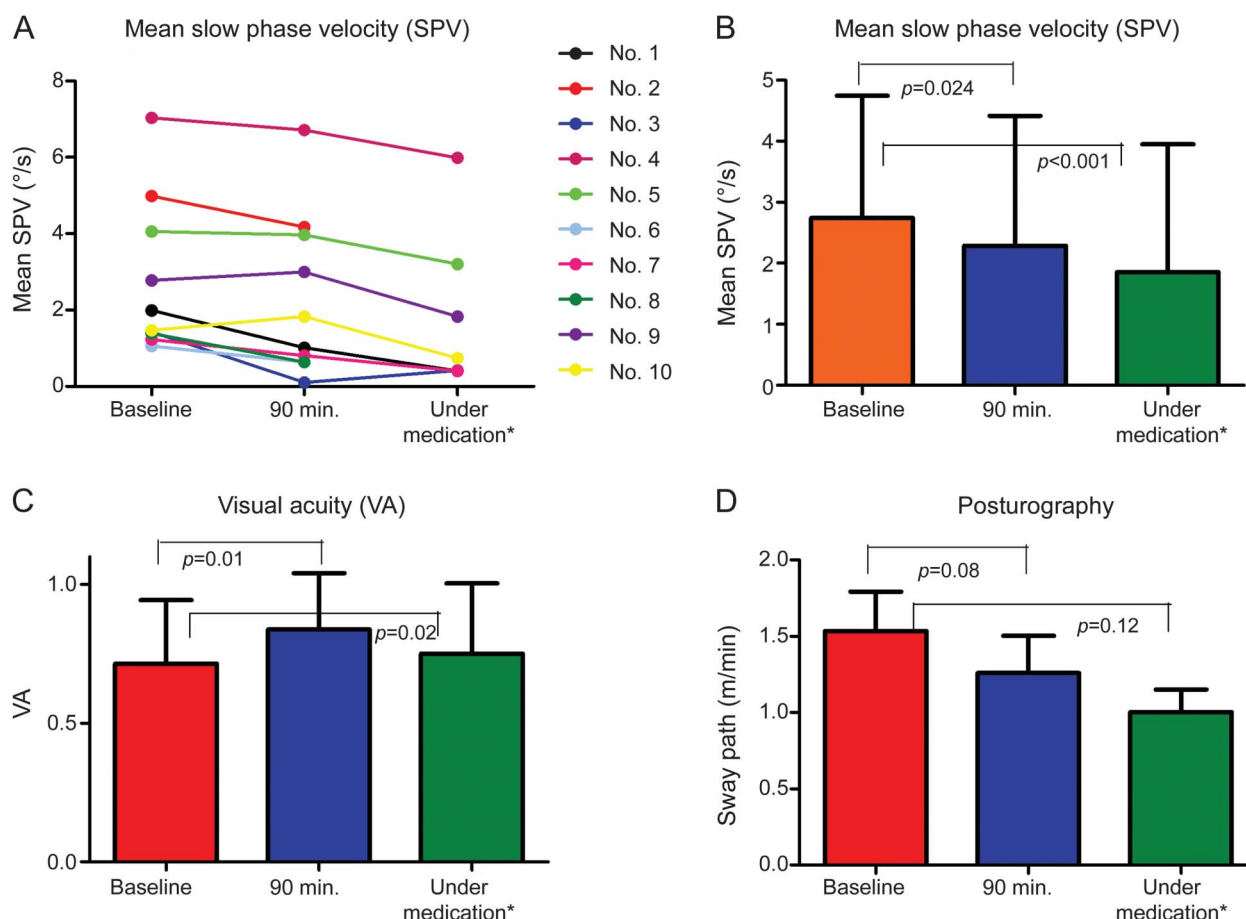
Side effects. All patients had normal blood test results. Fifty percent of patients reported abdominal discomfort during the treatment period (patients 5, 7, 8, 9, and 10). Patient 2 stopped treatment because of non-compliance, patient 6 because of hospitalization for formerly known atrial fibrillation, and patient 8 because of abdominal discomfort (see table 2). Regarding the Vestibular Disorders Activities of Daily Living Scale, there was no significant difference between the scores of the patients at baseline and under treatment

Figure 1 Original recordings of vertical eye positions of different patients taking chlorzoxazone 500 mg 3 times a day



Original recording of the vertical eye position with mean slow-phase velocity of downbeat nystagmus of 3 different patients (4, 7, and 10) at the different time points: before medication, 90 minutes after first administration of chlorzoxazone (CHZ) 500 mg 3 times a day (tid), and on medication with CHZ 500 mg tid for 1 or 2 weeks. *Nonresponder, treatment period of 1 week. Patients 7 and 10 (responder) received CHZ for 2 weeks.

Figure 2 Effect of treatment with chlorzoxazone 500 mg 3 times a day in patients with downbeat nystagmus



Effect of chlorzoxazone (CHZ) on mean slow-phase velocity (SPV) (A, B), visual acuity (VA) (C), and posturography (D). Measurements performed at baseline, 90 minutes after medication, and on medication (1 or 2 weeks of CHZ 500 mg 3 times a day). Posturography only shown in condition 1: upright position with eyes open and head inclined backward (30°) on firm ground. *On medication: 1 or 2 weeks under CHZ 500 mg 3 times a day. VA improved on medication.

($p = 0.691$), but a positive tendency was shown in some patients (3, 4, 5, 9, and 10).

DISCUSSION This observational proof-of-principle pilot study showed that CHZ caused a significant decrease of intensity of DBN and an improvement of VA. Postural imbalance also improved. Forty percent of patients had a decrease of $\geq 40\%$ of mean SPV during treatment with CHZ. In 60% of patients, mean SPV decreased by $>50\%$ and in 70% by $>40\%$ during treatment with 3,4-DAP.¹⁵ In comparison, 40% of the patients receiving 4-AP showed a decrease of mean SPV of $>50\%$.¹ Thus, CHZ at the doses used might be less effective than aminopyridines.^{1,2,15} Animal experiments suggest that CHZ could be more effective than 4-AP.^{6,7}

What is the assumed mechanism of CHZ in DBN? In the tottering mouse, an animal model of EA2, it was shown that CHZ (as well as 4-AP) can prevent attacks (without an additive effect)^{6,7}; oral administration of CHZ also improved baseline motor performance and reduced the severity and duration of

episodes of dyskinesia without producing any adverse effects. Single-cell recordings revealed that in this animal model the firing rate of PCs is very irregular. The loss of the precision of pace-making in EA2 is the consequence of reduced activation of calcium-dependent potassium channels by the smaller calcium current. As shown in animal experiments, despite contrasting pharmacologic effects of 4-AP (potassium-channel blocker) and CHZ (unspecific SK-channel activation), both can restore the precision of pace-making of PCs.⁷ For CHZ, the assumed pharmacologic mechanism is an increase in the magnitude of the potassium currents via SK channels.⁷ This may also be relevant in DBN, which is assumed to be caused by an impaired function of PCs in the flocculus.⁴ In this observational study, patients received CHZ, 500 mg 3 times a day. The US Food and Drug Administration recommends an adult daily allowance of 250–750 mg orally 3–4 times a day.¹⁰ With our dosage, 50% of patients already reported abdominal discomfort, which was probably due to the high initial dose. Perhaps patients would tolerate the drug

Table 2 Changes of clinical measurements on medication with CHZ 500 mg 3 times a day

Measurement ^a	SPV (°/s) ^b	Sway path (m/min) (cond. 1/cond. 2) ^c	Visual acuity	VDADL score	Side effects
Patient 1					
1	1.99 ± 3.92	2.46/5.58	0.70	2.9	None
2	1.01 ± 2.41	2.15/3.93	0.70		
3	0.40 ± 1.19	1.44/3.56	0.70	3.9	
4					
Patient 2					
1	4.99 ± 1.48	3.43/3.40	0.55	3.2	Stopped medication because of noncompliance
2	4.18 ± 0.95	1.92/2.64	0.55		
3					
4	5.13 ± 1.44		0.55		
Patient 3					
1	1.09 ± 0.72	1.18/2.67	1.00	2.4	None
2	0.10 ± 0.35	1.16/2.39	1.00		
3	0.26 ± 0.36	1.03/2.00	1.00	1.6	
4					
Patient 4					
1	7.04 ± 5.94	0.89/2.56	0.50	4.1	None
2	6.72 ± 0.92	0.45/0.95	0.90		
3	5.99 ± 0.76	0.74/1.76	0.80	3.9	
4					
Patient 5					
1	4.06 ± 0.57	1.06/7.76	0.58	4.0	Abdominal discomfort after increase of dose (after 1 wk)
2	3.97 ± 0.70	0.58/7.43	0.60		
3	3.33 ± 0.17	0.62/4.76	0.60	3.4	
4	4.15 ± 0.65	1.74/4.85	0.58		
Patient 6					
1	1.06 ± 0.37	1.00/2.26	0.68	4.0	None
2	0.64 ± 1.02		0.70		
3	1.66 ± 0.68	1.30/2.95			
4			0.70		
Patient 7					
1	1.23 ± 0.70	1.76/2.85	0.68	3.8	Abdominal discomfort
2	0.81 ± 0.60	1.55/2.55	0.89		
3	0.11 ± 0.40		0.70		
4					
Patient 8					
1	1.39 ± 1.10	1.42/2.54	1.00	5.9	Stopped the treatment because of abdominal discomfort
2	0.06 ± 1.00		1.00		
3					
4					

Continued

Table 2 Continued

Measurement ^a	SPV (°/s) ^b	Sway path (m/min) (cond. 1/cond. 2) ^c	Visual acuity	VDADL score	Side effects
Patient 9					
1	2.78 ± 0.90	0.66/2.64	1.00	5.6	Abdominal discomfort
2	3.00 ± 0.70		1.00		
3	1.83 ± 0.60	1.18/1.96	1.00	2.5	
4					
Patient 10					
1	1.47 ± 0.80	0.95/1.78	0.78	2.4	Abdominal discomfort
2	1.83 ± 1.10	1.01/2.31	1.00		
3	0.74 ± 0.60		1.00	2.3	
4					

Abbreviations: CHZ = chlorzoxazone; cond. = condition; SPV = slow-phase velocity; VDADL = Vestibular Disorders Activities of Daily Living.

^aTime periods: 1 = baseline; 2 = 90 min after first administration; 3 = after 1 or 2 wk under CHZ 500 mg 3 times a day; 4 = after washout period without medication for at least 4 wk.

^bMean ± SD SPV of downbeat nystagmus of patients treated with CHZ at different time points.

^cCond. 1 = upright position with eyes opened and inclined head on firm ground; cond. 2 = upright position with eyes opened and inclined head on foam ground.

better with a slower titration. Furthermore, CHZ is not only selective for SK channels but also activates large-conductance potassium ion channels (BK channels).¹⁶ As selective drugs for SK channels become available, they may be of superior therapeutic efficacy. As a selective positive modulator of calcium-activated potassium channels with positive effects in mouse models of spinocerebellar ataxia type 2 has become available, this would therefore also be a potential candidate for the treatment of DBN.¹⁷

This proof-of-concept pilot study has some limitations. First, it was not a randomized placebo-controlled clinical trial. Second, only one dosage was tested. Third, the number of patients was low. Fourth, there were not sufficient data for the washout period.

This study shows a significant effect of the nonselective SK-channel activator CHZ in DBN. This is thereby a new therapeutic principle that could be of relevance not only for the treatment of DBN but also for the treatment of other cerebellar disorders, e.g., EA2¹⁸ or cerebellar gait disorders,¹⁹ which also respond to aminopyridines. Thus, CHZ could be an alternative symptomatic treatment option for patients with DBN, in whom the use of aminopyridines is limited. It is necessary to further evaluate the effects of CHZ on DBN in a placebo-controlled, dose-finding trial with additional outcome measures, in particular quality of life.

AUTHOR CONTRIBUTIONS

K.F. and J.C.: drafting/revising the manuscript for content, including medical writing, study concept, analysis and interpretation of data, acquisition of data. S.B.: revising the manuscript for content, analysis and interpretation of data, acquisition of data. J.T.: drafting/revising the manuscript for content, including medical writing for content. S.K.: revising manuscript for content.

E.S.: drafting/revising the manuscript for content, acquisition of data. R.S., K.J., and R.K.: drafting/revising the manuscript for content, including medical writing for content. M.S.: drafting/revising the manuscript for content, including medical writing for content, critical revision of the manuscript for important intellectual content, study concept/design.

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